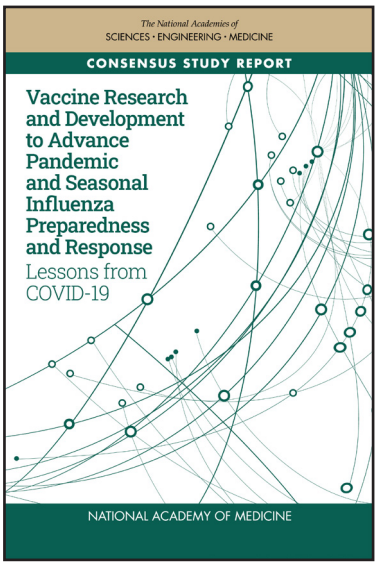
Consensus Study Report

NOVEMBER 2021

HIGHLIGHTS

Vaccine Research and Development to Advance Pandemic and Seasonal Influenza Preparedness and Response: Lessons from COVID-19



The global response to the COVID-19 pandemic has led to the emergence of new capabilities, technologies, processes, and policies for responding to the threat of major infectious diseases. While COVID-19 currently dominates the conversation around vaccines, seasonal and pandemic influenza remain critical threats. In fact, as many as 650,000 respiratory-related deaths per year worldwide result from influenza. There is a need for more effective influenza vaccines and modern manufacturing technologies that are adaptable and scalable to meet demand during a pandemic. The rapid development of COVID-19 vaccines has demonstrated what is possible with extensive data sharing, researchers who have the necessary resources and novel technologies to conduct and apply their research, rolling review by regulators, and public–private partnerships.

This report provides recommendations from an expert committee—convened under the auspices of the National Academy of Medicine and the National Academies of Sciences, Engineering, and Medicine—on how to leverage the knowledge gained from the COVID-19 pandemic to optimize vaccine research and development (R&D) to support the prevention and control of seasonal and pandemic influenza. The committee's findings address four dimensions of vaccine R&D: (1) basic and translational science, (2) clinical science, (3) manufacturing science, and (4) regulatory science.

BASIC AND TRANSLATIONAL SCIENCE

During large-scale virus outbreaks, the rapid development of effective vaccines is needed to curb the spread and toll of the virus. Continuous funding for vaccine R&D is vital for pandemic preparedness, but is often not sufficient until there is a clear, imminent pandemic threat. A reactionary funding model stalls R&D progress and leaves the world ill prepared for the rapid spread of pandemic viruses. Novel vaccine platforms have the potential to improve the effectiveness and speed with which vaccines are produced. As seasonal egg-based influenza

NATIONAL ACADEMY of MEDICINE

The National Academies of SCIENCES ENGINEERING MEDICINE

vaccines have low to moderate efficacy and require annual updates, significant funding is necessary to develop novel platforms and technologies that may lead to vaccines that are more efficacious. COVID-19 has resulted in a paradigm shift in vaccine technology, presenting benefits for the rapid development of pandemic vaccines and improving seasonal influenza vaccine effectiveness. This will require building additional production capacity to include accommodating regions where capacity may be limited.

Recommendations on basic and translational science:

- The U.S. Department of Health and Human Services (HHS) and other relevant governmental and funding agencies domestically and abroad should invest in basic and translational research to develop a diverse array of influenza vaccines, using different platforms, viral targets, adjuvants and delivery systems.
- The World Health Organization (WHO) should advocate and coordinate with multilateral stakeholders, governments, funding agencies, the vaccine industry, and philanthropic organizations to build global capacity for robust and internationally comparable pre-clinical, clinical and immunological assessments of influenza vaccine candidates.
- International research networks should support, plan, and conduct international clinical trials and field studies to compare emerging vaccines with standard vaccines in geographically, demographically, and immunologically diverse populations.
- National regulators should engage with the vaccine industry and academic researchers to develop, standardize, and implement innovative assays to evaluate vaccines that induce immunity through mechanisms other than strain-specific neutralizing antibodies.

CLINICAL SCIENCE

Research for the next generation of influenza vaccines requires extensive investment in clinical development. Given the costly nature of conducting clinical studies, many industries see little incentive. The expansion of clinical trials globally, particularly in low- and middle-income countries (LMICs), can decrease the risk of such large investments and fill the clinical funding gap. Clinical studies of influenza vaccines need to represent the diversity of the population studied, and early studies should prioritize high-risk groups. Population-based studies should measure differential effects in subpopulations, with consideration of characteristics such as race/ethnicity, socioeconomic status, age, pre-existing medical conditions, and diversity within and across countries. Coordinated global pharmacovigilance systems are necessary to ensure vaccine effectiveness and safety data are complete and up to date. It is critical that for LMICs participation in such systems be established early so the needs of their diverse populations are adequately represented in important decisions.

Recommendations on clinical science:

- WHO, in collaboration with national public health agencies, should conduct burden of disease studies in LMICs to understand factors like the health and economic burden of influenza illness and barriers to immunization in adult, pregnant, and pediatric populations.
- The International Coalition of Medicines Regulatory Authorities (ICMRA) and WHO, in partnership with national regulatory and public health agencies, should invest in global data infrastructure and capacity building to conduct real-time sentinel surveillance of vaccine safety and effectiveness. Data should be shared across sites.
- ICMRA and WHO should ensure international coordination and collaboration on the timely and transparent review of vaccine safety data during epidemics and pandemics.

MANUFACTURING SCIENCE

The majority of vaccine manufacturing capacity is in high-income countries (HICs). Expanding manufacturing capacity in LMICs can help avoid the delayed rollout of vaccines in LMICs. It is vital that these models not only be sufficient but also self-sustainable to ensure that production can keep up with the urgency of demand in pandemic conditions. It could also shorten the time to control the pandemic and limit the spread of viral variants. Exploring novel platforms for vaccine production can also lower the risk of supply chain shortages. Public-sector investments and improvements to data-sharing infrastructure can aid manufacturing centers' ability to mobilize quickly during the next pandemic. Financial aid may also incentivize vaccine manufacturers to assume more risk in building infrastructure. Eligibility for such funding would be contingent upon participation in R&D, data sharing, technology adaptation, and training activities with international partners.

Recommendations on manufacturing science:

- HHS and WHO should develop a plan for a sufficient and self-sustainable global supply of influenza vaccines for pandemics, including
  - Convening, supporting, and encouraging multinational, public and private vaccine manufacturers to benchmark, prioritize, and harmonize influenza vaccine manufacturing.
  - Enhancing and expanding support of the global influenza vaccine manufacturing network, creating manufacturing hubs for greater collaboration, and building capacity to address challenges in manufacturing in LMICs.
- Vaccine manufacturers should take a risk-based approach for pandemic influenza preparedness. This approach would be most effective if incentivized, and could include
  - Participating during R&D, data sharing, technology adoption, and training activities with international partners.
  - Growing internal capacity to assess the production needs and their risks.
  - Using scientific evidence to design strategies to reduce risks (e.g., WHO prequalification, licensing, marketing, etc.).
  - Formalizing technology transfer activities and considering timelines and the outcomes for equitable costs, access, and distribution.

REGULATORY SCIENCE

Regulators should develop comprehensive and transparent guidelines for how to conduct preclinical and early clinical trials between pandemics and develop pathways for the rapid review of vaccines for pandemic strains. Such efforts should include provisions for optimizing passage through regulatory pathways, including improved understanding of correlates of protection. Regulatory agencies should work closely with public health organizations to ensure that the public receives accurate and streamlined messaging about vaccine development and approvals. As a gesture of goodwill, vaccine manufacturers are encouraged to share vaccine trial results and updates in regulatory review to identify how to mitigate inefficiencies faced through vaccine development and approval processes.

Recommendations on regulatory science:

- The U.S. Food and Drug Administration (FDA) and other national regulators working with the scientific community and pharmaceutical industry should enhance comprehensive guidance for the development of influenza vaccines on novel platforms through emergency use authorization to full licensure.
- FDA and other national regulators should commit to transparency in the oversight of clinical trials and the review of data, authorization, and approval of pandemic influenza vaccines, including the release of facility inspection findings, clinical trial protocols, and clinical data.
- WHO and ICMRA should encourage and support coordination between regulatory and public health agencies when announcing different decisions on the same or similar vaccines.
- Vaccine manufacturers should adopt a code of conduct for communications regarding vaccine trial results and other matters emphasizing the critical role of regulatory review.

CONCLUDING REMARKS

Lessons from the COVID-19 response can help enhance preparedness for a future influenza pandemic. Vaccine R&D has taken major steps forward in 2020 and 2021, yet, while vaccines were available for COVID-19 within 1 year of its onset, there is significant room for improvements that would speed up vaccine R&D and manufacturing. Having vaccines earlier and widely and equitably available—including through building vaccine production and distribution capacity in LMICs—in a future influenza pandemic could significantly reduce both the burden of disease and the social and economic consequences domestically and around the world.

This is one of four studies conducted under the **Advancing Pandemic and Seasonal Influenza Vaccine Preparedness and Response Initiative,** which explores how the scientific and technological breakthroughs throughout the COVID-19 pandemic could inform and advance future pandemic and seasonal influenza vaccine preparedness and response efforts.

Committee on Vaccine Research and Development Recommendations for Advancing Pandemic and Seasonal Influenza Preparedness and Response

Enriqueta Bond (*Co-Chair*)
QE Philanthropic Advisors

Kanta Subbarao (*Co-Chair*)
World Health Organization Collaborating Centre for Reference and Research on Influenza

Maria Elena Bottazzi
National School of Tropical Medicine; Texas Children's Center for Vaccine Development, Baylor College of Medicine; Vaccines and Therapeutics Taskforce, Lancet Commission on COVID-19

Rebecca Jane Cox
University of Bergen and Haukeland University Hospital

Annette Fox
World Health Organization Collaborating Centre for Reference and Research on Influenza

Florian Krammer
Icahn School of Medicine at Mount Sinai

Grace Lee
Stanford University School of Medicine

John Martin (*until March 30, 2021, deceased*)
Gilead Sciences

Joshua Sharfstein
Johns Hopkins Bloomberg School of Public Health

Milagritos Tapia
University of Maryland School of Medicine

Study Staff

Hoda Soltani
Study Director

Emilie Ryan-Castillo
Senior Program Assistant

Elizabeth Ashby
Research Associate

Hannah Collins
Research Associate

Patricia Cuff
Senior Program Officer

Julie Pavlin
Senior Director, Board on Global Health

Consultant

Maartje Wouters
Science Writer

To read the full report, please visit
https://www.nationalacademies.org/flu-vaccine-R-and-D

NATIONAL ACADEMY of MEDICINE

The National Academies of SCIENCES ENGINEERING MEDICINE